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(21) International Application Number: PCT/US00/04636 (22) International Filing Date: 24 February 2000 (24.02.00) (30) Priority Data: 09/259,133 26 February 1999 (26.02.99) US (71) Applicant: ANDRX PHARMACEUTICALS, INC. [US/US]; Suite 201, 4001 S.W. 47th Avenue, Fort Lauderdale, FL 33314 (US). (72) Inventors: CHEN, Chih-Ming; 10680 S.W. 40th Manor, Davie, FL 33328 (US). XIE, Jianbo; Apartment B-7, 6630 Building - 5, Davie, FL 33314 (US). JAN, Steve; 512 N.W. 120th Drive, Coral Springs, FL 33071 (US). (74) Agent: COSTIGAN, James, V.; Hedman, Gibson & Costigan, P.C., 1185 Avenue of the Americas, New York, NY 10036 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: CONTROLLED RELEASE BUPROPION FORMULATION			
(57) Abstract A controlled release dosage form of bupropion hydrochloride which comprises: (a) a first pellet having a core of bupropion hydrochloride and hydroxypropyl methylcellulose at a weight ratio of 10:1 to 30:1 and a coating of a mixture of an acrylic resin which is soluble in acidic media and ethyl cellulose; (b) a second pellet having a core of bupropion hydrochloride and hydroxypropyl methylcellulose at a ratio of 10:1 to 30:1; an inner coating of a mixture of an acrylic resin which is soluble in acidic media and a water insoluble polymer and an outer coating which comprises an enteric coating polymer.			

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CONTROLLED RELEASE BUPROPION FORMULATION

BACKGROUND OF THE INVENTION:

5 The present invention relates to a controlled release formulation of bupropion hydrochloride. The compound bupropion hydrochloride is described in U.S. 3,819,706 as an antidepressant.

10 U.S. 5,427,798 describes a controlled release formulation of bupropion which based on a ratio of hydroxypropyl methylcellulose which is 1 part of bupropion to 0.19 to 1.1 parts of hydroxypropyl methylcellulose. U.S. 5,358,970 discloses a formulation of bupropion hydrochloride which is stabilized with a stabilizer which has specific acid properties under particular test
15 conditions. RE 33,994 is limited to a bupropion hydrochloride controlled release formulation which releases 10-45% of bupropion hydrochloride within two hours; 25-70% bupropion hydrochloride within 4 hours and 40-90% of bupropion hydrochloride within six hours. Wellbutrin SR is
20 a commercially available twice a day dosage form of bupropion hydrochloride which contains carnauba wax, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

25 The applicants have discovered that a two pellet controlled release formulation may be employed to provide a dosage formulation which has a controlled release profile which is bioequivalent to Wellbutrin SR but has a distinctly different in vitro release profile than
30 Wellbutrin SR.

SUMMARY OF THE INVENTION

35 The present invention provides a novel dosage form of bupropion hydrochloride which comprises:

(a) a first pellet having a core which comprises bupropion hydrochloride and hydroxypropyl methylcellulose at a weight ratio of 10:1 to 30:1 and a coating which comprises a

mixture of an acrylic resin which is soluble in acidic media and ethyl cellulose;

(b) a second pellet having a core which comprises bupropion hydrochloride and hydroxypropyl methylcellulose at a ratio of 10:1 to 30:1, preferably 20:1; an inner coating which comprises a mixture of an acrylic resin which is soluble in acidic media and a water insoluble polymer and an outer coating which comprises an enteric coating polymer.

Generally, the weight ratio of the first pellet to the second pellet will be from 90:10 to 30:70 although a weight ratio of 80:20 is preferred.

Accordingly, it is a primary object of this invention to provide a pharmaceutical dosage formulation of bupropion which is suitable for twice a day administration.

It is also an object of this invention to provide a hydrogel-free pharmaceutical dosage form of bupropion hydrochloride which is bioequivalent to dosage forms of bupropion hydrochloride which have a hydrogel component.

It is also an object of this invention to provide a stable dosage form of bupropion hydrochloride which is based on a two pellet-membrane coated dosage form.

These and other objects of the invention will become apparent from a review of the appended specification.

DETAILED DESCRIPTION OF THE INVENTION

The bupropion hydrochloride formulation of the invention is preferably based on active pellets having a core forming inert component which may comprise non-pareil sugar seeds (sugar spheres, USP XXII) having an average size of from 14 to 35 mesh, preferably about 30 to 35 mesh. The core forming inert component is coated with a formulation which comprises bupropion hydrochloride and hydroxypropyl methylcellulose. A sufficient amount of the coating is applied to provide the dosage of bupropion hydrochloride, i.e. 50mg to 300mg.

To form pellet A, the active pellet is then coated with a seal coat which may comprise a mixture of hydroxypropyl methylcellulose and polyethylene glycol. The hydroxypropyl methylcellulose may have a viscosity of 5 mPa's at a 2wt% conc. in water at 20°C. The polyethylene glycol may have a number average molecular weight of from 200 to 2000 although a number average molecular weight of 400 is preferred. Generally a ratio of 2:1 to 6:1 of hydroxypropyl methylcellulose to polyethylene glycol may be applied as a 3 to 7wt% solution in a solvent such as ethanol, isopropyl alcohol, water, mixtures thereof and the like.

The seal coat is then coated with a release modifying coating which comprises a mixture of an acrylic resin which is soluble in acidic media and a water insoluble polymer. The water insoluble polymer may comprise a cellulosic polymer such as ethylcellulose, cellulose acetate and the like. The release modifying seal coating may comprise a weight ratio of acrylic resin which is soluble in acidic media to water insoluble polymer of about 1:4 which is applied from a 3 to 7wt% solution of isopropyl alcohol, ethanol, acetone, mixtures thereof and the like to form a coating.

A useful acrylic resin which is soluble in acidic media is Eudragit E which is a cationic copolymer of dimethylaminoethyl methacrylate and neutral methacrylic acid esters having a mean weight average molecular weight of 150,000.

If desired a seal coat of a film forming polymer such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose or the like may be applied to form a coating.

To form pellet B, pellet A is coated with a first coating of hydroxypropyl methylcellulose which is applied from a 5wt% solution of ethanol, water or mixtures thereof to form a coating. An enteric coating is then placed on the coating of the hydroxypropyl methylcellulose. The enteric

coating polymer may be selected from the group consisting of shellac, methacrylic acid copolymers, (Eudragit S or L) cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, 5 cellulose acetate trimellitate, polyvinyl acetate phthalate or mixtures thereof. Cellulose acetate phthalate is preferred. The thickness of the coating is selected to provide the desired release rate depending on the thickness of the coating and the particular coating. The enteric 10 coating may be applied as a 3 to 7wt% solution of the enteric polymer in acetone, ethanol, isopropyl alcohol or mixtures thereof.

Other auxiliary coating aids such as a minor amount (1-5wt% based on the active core component and the 15 total weight of the final coating) of a plasticizer such as acetyltributyl citrate, triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, 20 diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol (molecular weight of from 380 to 420), propylene glycol and mixtures thereof in combination with an antisticking agent which is selected from the group 25 consisting of an alkaline earth metal stearate, such as magnesium stearate or calcium stearate, or talc. The antisticking agents can be used alone or in combination.

The cores are formed by spraying the non-pareil seeds with an aqueous or non-aqueous suspension which 30 contains the bupropion hydrochloride and the hydroxypropyl methylcellulose. The suspension medium may comprise any low viscosity solvent such as isopropyl alcohol, ethanol, water, mixtures thereof and the like. When fluids such as water are employed, this will usually require a weight of 35 fluid which is about seven times the weight of the dry components of the coating composition.

It is preferred to dry each coating before

applying a second coating. A color imparting agent may be added to the enteric coating mixture or a rapidly dissolving seal coat containing color may be coated over the enteric coating layer provided that the seal coat is compatible with and does not affect the dissolution of the enteric coating layer.

Pellets A and pellets B are blended together to obtain a finished product having the following in vitro release profile:

50 to 80 wt% released after 2 hours in SGF (pH 1.5);
70 to 95 wt% released after 4 hours in SGF (pH 1.5);
not less than 80 wt% released after 6 hours in SGF (pH 1.5);
as determined in a USPXXII Type 2 apparatus, at 37°C and 50rpm.

The pellets may be placed in a gelatin capsule or they may be made into tablets by first adding from 25 to 40wt% of a solid pharmaceutically acceptable tablet excipient which will form a compressible mixture with pellets A and pellets B which may be formed into a tablet without crushing pellets A or pellets B, and optionally an effective amount of a tablet disintegrating agent and a lubricant. The solid pharmaceutically acceptable tablet excipient may comprise lactose, dextrose, mannitol, calcium phosphate, microcrystalline cellulose, kaolin, powdered sucrose or mixtures thereof. The tablet disintegrant may comprise croscopovidone, croscarmellose sodium, dry starch, sodium starch glycolate and the like.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

Active pellets of bupropion hydrochloride are formed by placing sugar spheres in a fluidized bed coater and spraying a suspension containing bupropion hydrochloride and hydroxypropyl methylcellulose onto the

sugar spheres. The formulation for making the active pellets has the following composition:

bupropion hydrochloride, USP	9760 g
5 hydroxypropyl methylcellulose E5	480 g

The bupropion hydrochloride, hydroxypropyl methylcellulose and about 48,000g of water and isopropyl alcohol (3:1) are mixed with a mechanical mixer until the materials are dissolved.

9760.0g of non-pareil sugar spheres (NF 30/35 mesh) are placed in the fluidized bed coater and the suspension containing the bupropion is coated at a product temperature of 30-50°C; an atomization pressure of 2- 3.5 bar and a pump rate of 20-200 ml/minute, starting with a slow rate of pumping to avoid agglomeration and increasing the rate of pumping consistent with the avoidance of the formation of agglomerates.

After coating is complete the pellets are dried at a temperature of 50°C until the loss on drying is less than 1 wt% The pellets are then screened through a #18 mesh screen and coated with the following formulation:

25 hydroxypropyl methylcellulose	1342g.
polyethylene glycol 400	335g.

After drying the pellets, a further coating is applied as follows:

ethyl cellulose E100	4124g.
acrylic polymer (Eudragit E-100	1694g.

35

The coated pellets are dried to complete the formation of pellets A.

Pellets B are formed by coating pellets B as follows:

Pellets A	11,000g
hydroxypropyl methylcellulose	256g

5

The hydroxypropyl methyl cellulose is dissolved in ethanol and applied to pellets A. Thereafter an enteric coating is applied as follows to form pellets B:

10	cellulose acetate phthalate	1228g
	acetyltributyl citrate	307g

A tablet is made by blending:

	Pellets A	51 parts by weight
15	Pellets B	14 parts by weight
	crospovidone XL-10	5 parts by weight
	microcrystalline cellulose PH102	29 parts by weight
	glyceryl monostearate	1 parts by weight

20 The tablets were compressed using a B-press
tableting machine, with a punch size of 0.4375"

. The tablets were tested according to the USP XXII
dissolution test (type 2, basket) at 50rpm, at 37° in SGF
(pH 1.5) to determine the percent of the drug dissolved
25 versus time:

Tablets

	Time (hr)	Percent Dissolved
30	0.5	13
	1.0	32
	2.0	62
	4.0	83
	6.0	92
35	8.0	98

Pellets A

	Time (hr)	Percent Dissolved
40	0.5	6

	1.0	40
	2.0	91
	4.0	98
	6.0	100
5	8.0	100

Pellets B

	Time (hr)	Percent Dissolved
	0.5	0
10	1.0	0
	2.0	1
	4.0	16
	6.0	54
	8.0	73

15

All of the components which are used in the present invention are used in amounts which are effective for the intended purpose for which the component is employed.

20

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

25

Claims:

1. A controlled release dosage form of bupropion
5 hydrochloride which comprises:
(a) a first pellet having a core which comprises bupropion
hydrochloride and hydroxypropyl methylcellulose at a weight
ratio of 10:1 to 30:1 and a coating which comprises a
mixture of an acrylic resin which is soluble in acidic
10 media and ethyl cellulose;
(b) a second pellet having a core which comprises bupropion
hydrochloride and hydroxypropyl methylcellulose at a ratio
of 10:1 to 30:1; an inner coating which comprises a mixture
of an acrylic resin which is soluble in acidic media and a
15 water insoluble polymer and an outer coating which
comprises an enteric coating polymer.
2. A controlled release dosage form of bupropion
hydrochloride as defined in claim 1 wherein the pellets are
20 combined in a capsule.
3. A controlled release dosage form of bupropion
hydrochloride as defined in claim 1 wherein the pellets are
combined in a tablet.
- 25 4. A controlled release dosage form of bupropion
hydrochloride as defined in claim 1 wherein the weight
ratio of the first pellets to the second pellets is from
90:10 to 30:70.
- 30 5. A controlled release dosage form of bupropion
hydrochloride as defined in claim 3 wherein
the tablet comprises the first pellets, the second pellets
and a solid pharmaceutically acceptable diluent.
- 35 6. A controlled release dosage form of bupropion
hydrochloride as defined in claim 3 wherein

the first pellets are formed on a core which comprises a sugar sphere.

7. A controlled release dosage form of bupropion hydrochloride as defined in claim 1 wherein the first pellets are formed on a core which comprises a sugar sphere.

8. A controlled release dosage form of bupropion hydrochloride as defined in claim 1 wherein the second pellets have a seal coating between the inner coating which comprises a mixture of an acrylic resin which is soluble in acidic media and a water insoluble polymer and the enteric coating.

9. A controlled release dosage form of bupropion hydrochloride as defined in claim 1 wherein the second pellets have an enteric coating which is selected from the group consisting of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, cellulose acetate trimellitate and polyvinyl acetate phthalate.

10. A controlled release dosage form of bupropion hydrochloride as defined in claim 1 wherein the second pellets have an enteric coating which comprises cellulose acetate phthalate.

11. A controlled release dosage form of bupropion hydrochloride which comprises:
(a) a first pellet having a core which is a sugar sphere coated with a mixture comprising bupropion hydrochloride and hydroxypropyl methylcellulose at a weight ratio of 10:1 to 30:1 and a coating which comprises a mixture of acrylic resin and ethyl cellulose;
(b) a second pellet having a core which is a sugar sphere

coated with a mixture comprising bupropion hydrochloride and hydroxypropyl methylcellulose at a ratio of 10:1 to 30:1; an inner coating which comprises an acrylic resin which and ethyl cellulose and an outer coating which
5 comprises cellulose acetate phthalate plasticized with acetyltributyl citrate.

12. A controlled release dosage form of bupropion hydrochloride as defined in claim 1 wherein the dosage form
10 has the following in vitro release profile:
50 to 80wt% released after 2 hours in SGF (pH 1.5);
70 to 95wt% released after 4 hours in SGF (pH 1.5);
more than 80wt% released after 6 hours in SGF (pH 1.5);
as determined in a USPXXII Type 2 apparatus, at 37°C and
15 50rpm.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04636

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/14, 9/52, 9/58

US CL : 424/497, 489, 490

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/497, 489, 490

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, HCAPLUS, WPIDS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,427,798 A (LUDWIG ET EL.) 27 JUNE 1995 (27.06.95).	1-12
A	US 5,508,040 A (CHEN) 16 APRIL 1996 (16.04.96).	1-12
A	US 5,472,708 A (CHEN) 05 DECEMBER 1995 (05.12.95).	1-12

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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